## REMARKS

Applicants appreciate the courtesies extended by Examiner Samuel A. Barts during an interview on March 8, 2004 with Applicant's attorneys, Allan A. Fanucci and Jeffrey A. Wolfson. The comments appearing herein summarize, and are substantially in accord with, those presented and discussed during the interview.

Claims 30, 32-37, 39-42, and 44-49, as amended, and new claims 50-52 are pending in this application for the Examiner's review and consideration. Claims 30 and 42 have been amended simply to rewrite claims 31 and 43, respectively, in independent form. Accordingly, claims 31, 38, and 43 have been canceled without prejudice to Applicants' rights to file one or more continuing applications directed to this or other subject matter. Claims 30 and 42 have also been amended to re-add the "H" (*i.e.*, hydrogen) and to recite that $R_3$ includes $C_{5\text{-}12}$ alkyl chains to correct typographical errors introduced into the chemical structure in a previous Amendment. The currently claimed structure is that which is supported by the originally filed application and claims, *e.g.*, originally filed claim 2 with respect to the alkyl range. Claim 47 is amended to depend correctly from claim 42, as it refers to the "agonist" of the prior claim rather than the "composition" of the prior claim. New claims 50-52 are dependent on claim 47 and simply combine currently pending claim features such as those from claims 39-41. As there are no new issues and these amendments are fully supported by the specification such that there is no issue of new matter, the claims should be entered into the application at this time.

Initially, Applicants discussed a Declaration Under 37 C.F.R. § 1.132 with the Examiner during the interview. This Declaration is being prepared and will be submitted in due course at the Declarant's earliest possible convenience.

Claims 30-49 were rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,434,295 to Mechoulam et al. ("Mechoulam-'295") on pages 2-4 of the Office Action. Applicants respectfully traverse the rejection.

Mechoulam-'295 discloses certain novel 4-phenylpinene derivatives. Mechoulam also utilizes those derivatives in pharmaceutical compositions that are useful in treating problems relating to the central nervous system ("CNS") (Col. 1, lines 9-14).

Initially, Mechoulam-'295 does not disclose or suggest the specific compounds, compositions, or CB2 agonists presently recited. In particular, Mechoulam-'295 does not disclose the claimed combination of $R_1$ and G groups. Furthermore, these

compounds provide surprising and unexpected results compared to the compounds that are disclosed in the Mechoulam-'295 patent.

The compounds synthesized by Mechoulam-'295 are non-psychotropic and, as such, are presumed not to bind to cannabinoid receptors at all. In fact, binding to CB1 receptors, which are the major receptors of the CNS, is what induces undesired psychotropic effects. This must be minimized or avoided in the design and selection of these compounds for therapeutic uses. Mechoulam-'295 does not even suggest or test any of the compounds disclosed in his patent for their ability to bind a peripheral receptor, *i.e.*, one that is not a major CNS receptor. In fact, Mechoulam-'295 fails to even disclose that its compounds, much less HU-308, would bind to either CB receptor.

In contrast, the present Applicants have unexpectedly discovered that the presently claimed compounds, compositions, and agonists bind selectively to CB2 receptors, *i.e.*, to bind to the peripheral non-CNS receptors that appear mainly on lymphocytes. As disclosed in the present invention, HU-308 binds CB2 with a Ki = 22.7 $\pm$ 3.9 nM and a specificity of above 400 fold relative to CB1 (*See, e.g.*, Specification at page 10, lines 22-23). Such a high binding affinity and selectivity confer a clear therapeutic potential to HU-308. This therapeutic potential is not disclosed or even mentioned anywhere in Mechoulam-'295, most likely because the compounds of Mechoulam-'295 are not disclosed to possess these binding affinity and selectivity properties.

Applicants further unexpectedly found that binding to CB2 receptors confers on these compounds a surprisingly beneficial effect when used in the treatment of CB2 mediated disorders, including hypertension, pain, GI disorders, and autoimmune diseases, as well as tumors expressing CB2 receptors. These unexpected benefits were not taught by Mechoulam-'295 or any other cited prior art references.

Indeed, a side-by-side comparison of the preferential CB2/CB1 receptor binding affinity of HU-308 with the closest prior art compound, *i.e.*, compound HU-255 of Mechoulam-'295, demonstrated the surprising and unexpected benefit with respect to this feature of the claimed invention. HU-255 is an intermediate of HU-259, and both are set forth in Mechoulam-'295 at Cols. 9-10. In this regard, Mechoulam-'295did not teach any activity or even any testing for HU-255 since this compound is merely presented as an intermediate in the synthesis of HU-259. If the HU-255 compound were believed to be a preferred one, or if it possessed highly advantageous benefits, Mechoulam certainly would have mentioned this. When HU-255 was eventually tested for binding to cannabinoid receptors, it was found to have an $IC_{50}$ of 36 nM for CB1 and an $IC_{50}$ of 5.6 nM for CB2 in

specific radioligand displacement assays. In other words, HU-255, the closest prior art compound, has no significant CB2/CB1 selectivity, *i.e.*, it has a ratio of only about 6. This is seventy-fold lower than that of the present HU-308 compound as disclosed in the specification. Clearly, the superior results for HU-308 are far from obvious or expected based on the disclosure of HU-255 in the Mechoulam-'295patent. HU-259 is almost as deficient, having an $IC_{50}$ ratio of only approximately 10 compared to an $IC_{50}$ ratio of at least 270 for HU-308.

The remaining compounds recited in the present claims are closely related lower alkyl or hydrogenated derivatives of HU-308. As such, the unexpected results for HU-308 also support the patentability of such compounds. Accordingly, the obviousness rejection is not applicable to any of the compounds that are recited in the present claims, and no *prima facie* case of obviousness has been stated on the record. In the alternative, if a *prima facie* case of obviousness has been stated, the Declaration make of record the surprising and unexpected results of testing already conducted that is commensurate in scope with the claimed compounds, compositions, and CB2 agonists that are sufficient to rebut even a contention of obviousness.

Furthermore, claim 40 is further distinguishable from the Mechoulam patent because it is directed to a CB2 specific agonist. As compounds of Mechoulam-'295 are not taught to possess this feature, there is no teaching or motivation for the ordinary-skilled artisan to even look to those compounds or to attempt any modifications thereof in an attempt to develop such agonists. Nor does Mechoulam-'295 provide a reasonable expectation of success in so doing. For these reasons, the claims are distinct from the prior art. As such, Applicants respectfully submit that the rejection under 35 U.S.C. § 103(a) has been overcome as to all pending claims and should be reconsidered and withdrawn.

In view of the above, the entire application is believed to be in condition for allowance, early notice of which would be appreciated. Should any issues remain, a personal or telephonic interview is respectfully requested to discuss the same in order to expedite the allowance of all the claims in this application.

Respectfully submitted,

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